

# Assessing the Impact of Serum Per- and Polyfluoroalkyl Substance Concentrations on Immune Function in an Industrialized Region of China

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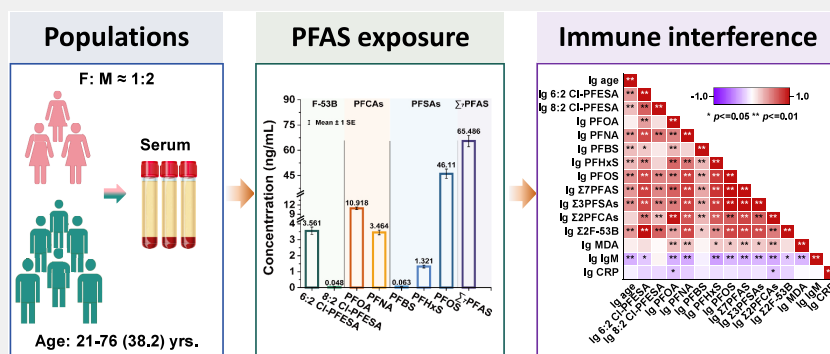
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**ABSTRACT:** This study investigates the presence and health implications of per- and polyfluoroalkyl substances (PFAS) in human serum samples collected from white-collar workers in an industrialized region of China. Our research offers fresh insights into the underexplored area of nonoccupational PFAS exposure among white-collar workers, shedding light on health risks linked to industrial PFAS pollution. Seven PFAS compounds were measured. Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) emerged as predominant pollutants, with  $\Sigma_7$ PFAS concentrations averaging 65.486 ng/mL. Gender differences showed higher serum  $\Sigma_7$ PFAS levels in males, and age-related analyses suggested PFAS accumulation over time, with higher concentrations in older groups. Additionally, significant correlations were found between PFAS concentrations and biomarkers of oxidative stress and immune interference, specifically malondialdehyde (MDA) and immunoglobulin M (IgM), indicating that PFAS exposure may contribute to oxidative damage and potential immunosuppression. The study highlights regional and international variations in PFAS serum concentrations, underscoring the influence of industrial activities on PFAS exposure and expanding on the established links between PFAS exposure and health outcomes. These findings call for targeted strategies to mitigate PFAS exposure in high-risk regions and warrant further research on PFAS health impacts, especially in regard to immune interference.

**KEYWORDS:** *Per- and polyfluoroalkyl substances, human serum, oxidative stress, immune interference*

## 1. INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) make up a large group of synthetic organic chemicals,<sup>1</sup> which have found wide industrial and commercial application since the 1940s.<sup>2</sup> An estimated 6420 tons of C<sub>4</sub>–C<sub>14</sub> perfluoroalkyl carboxylates (PFCAs) were forecast to be emitted during 2016 to 2030.<sup>3</sup> Restrictions on the manufacture and use of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) since 2002<sup>4–6</sup> have led to a shift of production and use toward short-chain PFAS (C < 8), like perfluorobutanesulfonate (PFBS) and perfluorohexanesulfonate (PFHxS), and other alternatives, such as perfluorononanoic acid (PFNA), potassium 9-chlorohexadecafluoro-3-oxanonane-1-sulfonate (6:2 Cl-

PFESA), and potassium 11-chloroeicosafuoro-3-oxaundecane-1-sulfonate (8:2 Cl-PFESA).<sup>7</sup>

The global distribution of PFAS in the environment and human populations has been documented in various studies.<sup>8–12</sup> Because of their environmental persistence, PFAS have been found around the world in surface water,<sup>8</sup> groundwater,<sup>13</sup> soil,<sup>14</sup> house dust,<sup>15</sup> landfills,<sup>16</sup> crops,<sup>17</sup> fish and

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other wildlife,<sup>18</sup> ambient air,<sup>16</sup> drinking water,<sup>9</sup> etc. Furthermore, PFAS has been widely found in human urine, serum, and other organs, varying from less than the limit of detection (LOD) to hundreds ng/mL,<sup>10,19–21</sup> highlighting the ubiquity of these compounds. Concerns about PFAS stem from their potential toxicity (including animal toxicity, immunotoxicity, endocrine disruption, carcinogenicity, etc.).<sup>19,22–25</sup> Multiple studies have reported significant associations between PFAS exposure and adverse immune outcomes in children and adults.<sup>26–28</sup> Despite the growing body of research, the relationships between serum PFAS concentrations and these health outcomes remain to be fully elucidated, especially in the context of varying geographical locations and population demographics. Simultaneously, the relationship of PFAS exposure with oxidative stress and immune functions is still not fully studied.

Oxidative stress serves as a critical initiator of immune responses, modulating the activation of immune cells and the release of inflammatory mediators, with studies showing that it can irreversibly damage cellular structures, leading to the formation of oxidation-specific epitopes (OSEs) that are recognized by innate immune cells, thus linking oxidative stress to inflammation and immune cell activation.<sup>29,30</sup> Malondialdehyde (MDA) is the product of lipid peroxidation and caused by oxidative stress;<sup>31</sup> thus, it is usually recognized as a biomarker of oxidative stress. C-reactive protein (CRP) is an acute-phase plasma protein involved in innate immune defense through its lectin-type binding role.<sup>32</sup> Simultaneously, the dominant pathway for activation of the complement system during innate immunity to *Streptococcus pneumoniae* is partially targeted by the binding of natural immunoglobulin M (IgM) to bacteria.<sup>30</sup> Thus, IgM and CRP are well-known biomarkers for immune conditions.<sup>33,34</sup>

In this study, seven PFAS, including two PFCAs (PFOA, PFNA), three perfluoroalkanesulfonates (PFASs:PFBS, PFHxS, PFOS), and two precursor compounds F-53B (6:2 Cl-PFESA, 8:2 Cl-PFESA) were measured in serum samples. By assessing the concentrations of these PFAS compounds in human serum, this research will provide valuable insights into the global exposure patterns of PFAS and their potential health implications toward oxidative stress and immune interference. Understanding the distribution and health effects of these compounds is essential for the development of effective strategies to mitigate PFAS exposure and protect public health. This study represents a significant step toward comprehensively characterizing the global burden of PFAS and their impact on human health.

## 2. MATERIALS AND METHODS

### 2.1. Chemical Standards and Reagents

Seven PFAS native standards (including PFOA, PFNA, PFBS, PFHxS, PFOS, 6:2 Cl-PFESA, and 8:2 Cl-PFESA) and nine isotopically labeled internal standards (including M8PFOA, M9PFNA, M3PFBS, MPPFHxS, M8PFOS and M4PFOS) were bought from Wellington Laboratories (Guelph, Canada) and Cambridge Isotope Laboratories (CIL, Andover, USA). Detailed information and PFAS structures are shown in Table S1.  $\beta$ -Glucuronidase from *Helix pomatia* (pH 5.0, 116 140 units/mL  $\beta$ -glucuronidase; 1021 units/mL sulfatase) was purchased from MilliporeSigma (USA). Methanol (MeOH, J.T. Baker, U.S.), ammonium acetate (Merck, Germany), tetrabutylammonium hydrogen sulfate (TBAHS, J&K, China), methyl *tert*-butyl ether (MTBE, J&K, China), and sodium carbonate anhydrous (Aladdin, China) were all HPLC grade with purity > 99%. Ultrapure Milli-Q water (18.2 M $\Omega$ -cm, TOC = 2 ng/mL) was prepared in the

laboratory by an ultrapure water purification system (Milli-Q direct 8, Merck Millipore, Burlington, MA).

### 2.2. Sampling

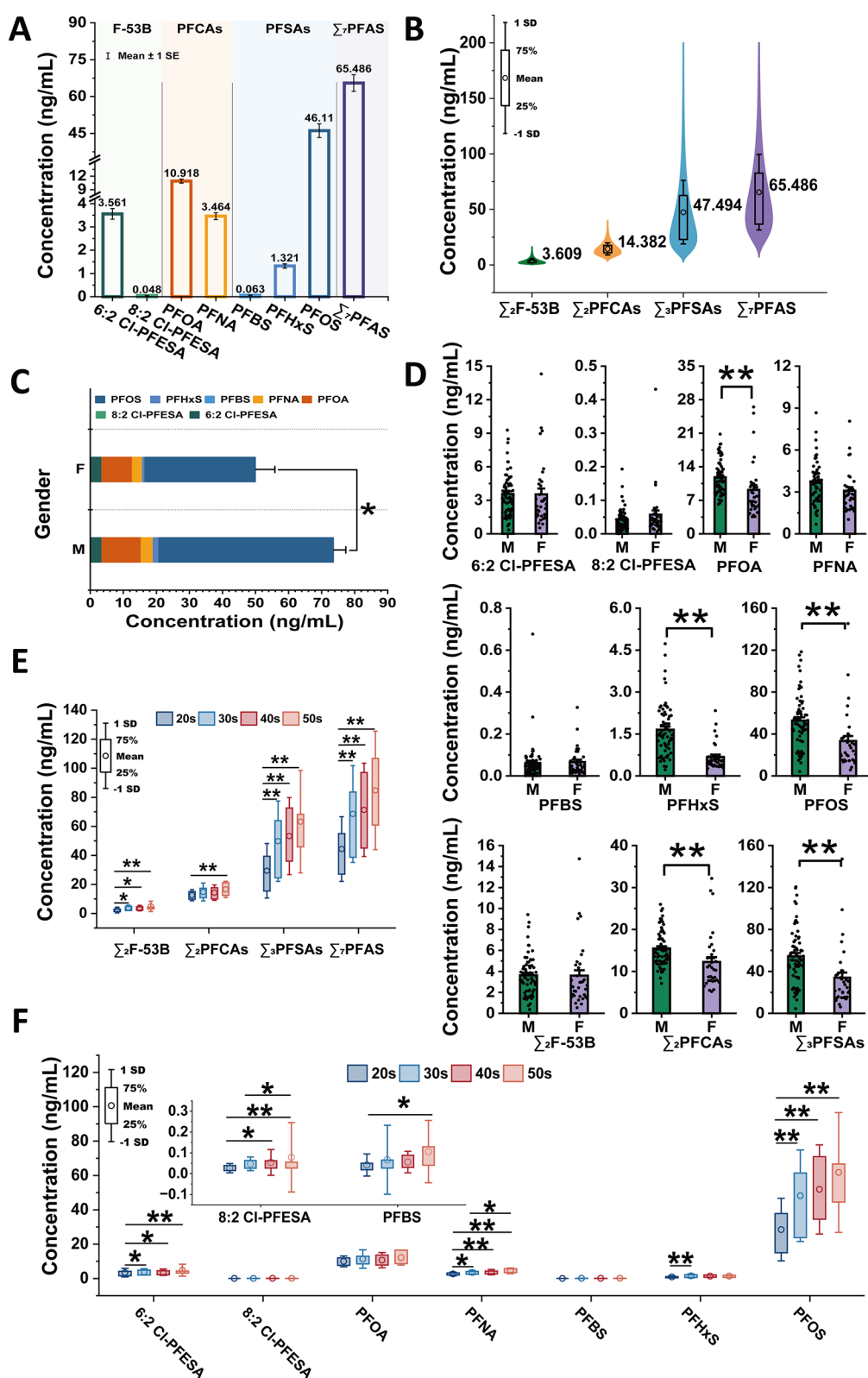
Owing to the importance for exploring nonoccupational human internal exposure to PFAS for the white-collar workers in industrial areas, in total, 100 samples of early morning fasting human blood were collected from white-collar workers in an industrialized region of China in 2017, and the blood collection was assisted by professional nurses in the health center of Shenzhen Hospital, Southern Medical University. All participants from the business enterprises presented nonoccupational exposure to PFAS, and they had no specific disease symptoms. The participants included 66 males and 34 females, with average ages of 39.0 (range of 21 to 76) and 36.5 (between 22 and 64), respectively. The whole set of samples was divided into four different age groups: 20s (21–30 yrs.), 30s (31–40 yrs.), 40s (41–50 yrs.), and 50s (above 50 yrs.). Detailed demographic information on the participants is shown in Table S2. Sample collection and storage were performed following the methods of Zhang et al.<sup>35</sup> Briefly, whole blood samples were collected in yellow-labeled polypropylene (PP) vacuum blood collection tubes, which were filled with inert separation adhesive that could promote the separation of serum and hemocytes and were centrifuged at 1200g for 5 min. After total deposition and separation, the upper serum was collected in 4 mL PP sterile cryogenic vials (Wheaton, USA) and stored at  $-80^{\circ}\text{C}$  until extraction. The sample collection was approved by the ethics committee of the Southern University of Science and Technology (20200076), and informed consent was obtained from each volunteer.

### 2.3. Sample Extraction for PFAS

Serum PFAS extraction was performed similarly to our previous study,<sup>35</sup> with minor modifications. Briefly, all serum samples were naturally dissolved at room temperature. Then, 0.5 mL of serum was pipetted into a 15 mL PP centrifuge tube (BD-Falcon, USA). 5.0 ng of each of our five internal standards (M8PFOA, M9PFNA, M3PFBS, MPPFHxS, and M8PFOS) were injected into each tube. Where possible, all native PFAS were quantified relative to the corresponding isotopically labeled internal standard, 6:2 Cl-PFESA and 8:2 Cl-PFESA quantified relative to M8PFOS. The procedural recovery tube was spiked with 100  $\mu\text{L}$  of mixed native standards (PFOA, PFNA, PFBS, PFHxS, PFOS, 6:2 Cl-PFESA, and 8:2 Cl-PFESA, 0.1 ng/ $\mu\text{L}$ ). After 1 h of equilibration, spiked urine samples were diluted with 2.0 mL of Milli-Q water, followed by buffering with 0.3 mL of 1.0 mol/L ammonium acetate buffer solution containing 348 units of  $\beta$ -glucuronidase, and digested in a  $37^{\circ}\text{C}$  water bath for 12 h. After digestion, sodium carbonate buffer solution (2.0 mL, 0.25 mol/L) and TBAHS (1.0 mL, 0.5 mol/L) were added for an ion-pair reaction. Liquid–liquid extraction was then performed twice with, respectively, 5 and 3 mL of MTBE. Each extraction consisted of 40 min of oscillation, followed by 10 min of centrifuge at 5000 rpm and transfer of the supernatant to a new clean 15 mL PP centrifuge tube. After that, the solution was evaporated nearly to dryness with a gentle nitrogen flow and then reconstituted with 400  $\mu\text{L}$  of MeOH and 100  $\mu\text{L}$  of M4PFOS in MeOH (1.0  $\mu\text{g}/\text{mL}$ , as a recovery determination (or syringe) standard). Finally, extracts were vortexed for 90 s until blending well and then transferred to glass autosampler vials ready for LC-MS/MS.

### 2.4. Instrument Analysis

PFAS were analyzed using an Agilent 1290-6470 Triple Quad LC/MS MS (Agilent, USA) with a C18 LC chromatographic column (2.1  $\times$  100 mm, 1.7  $\mu\text{m}$ , Thermo Fisher, USA). The 2 mmol/L  $\text{CH}_3\text{COONH}_4$  in Milli-Q water (phase A) and MeOH (phase B) were used as the LC mobile phases. The MS was operated in negative ESI plus Agilent Jet Stream ion mode and Dynamic MRM scan type with a nebulizer gas of 35 psi. Full details of the liquid chromatography and mass spectrometric parameters of LC-MS/MS analysis are presented in Tables S3 and S4.



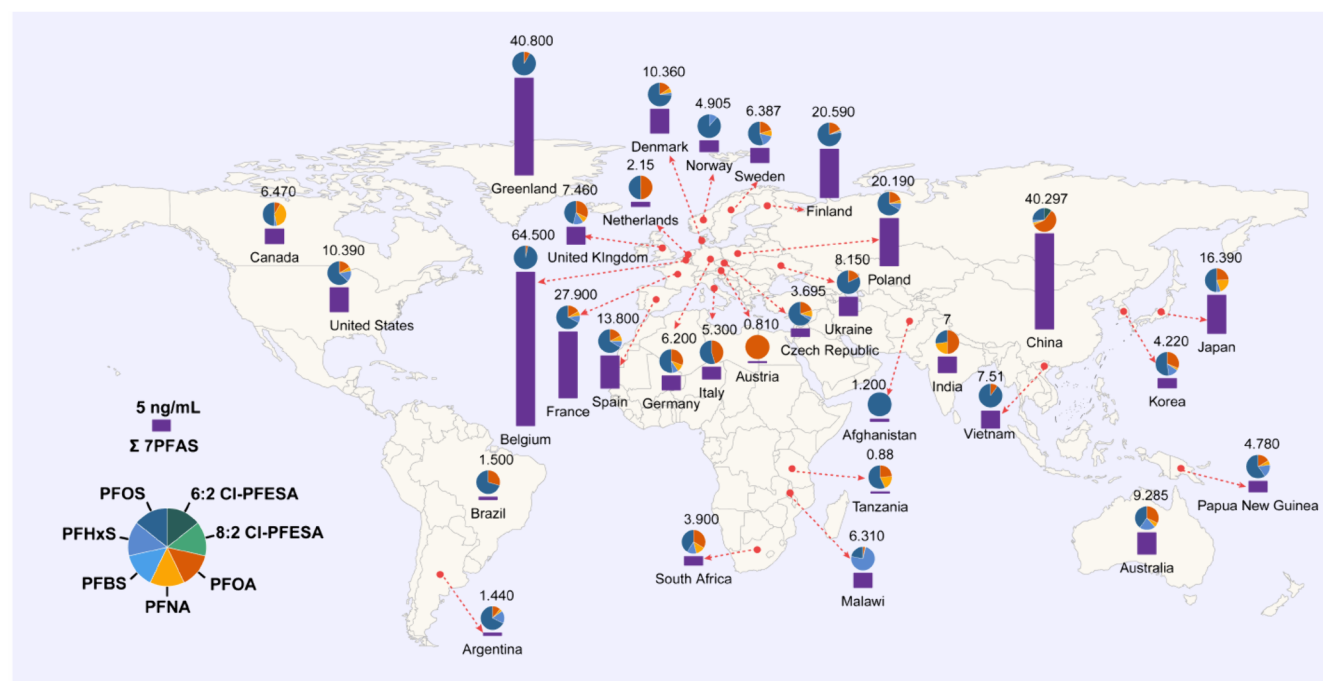
**Figure 1.** Individual (A) and subgroup (B) PFAS concentrations (mean) in human serum samples; gender differences of Σ-PFAS (C) and individual or subgroup PFAS (D) in this study; differences across age groups for concentrations of subgroup PFAS (E) and individual PFAS (F). The asterisks (\*\*,  $p < 0.01$ ; \*,  $p < 0.05$ ) indicate significant differences, and the y-error bar represents the standard error of the mean (SE).

## 2.5. QA and QC

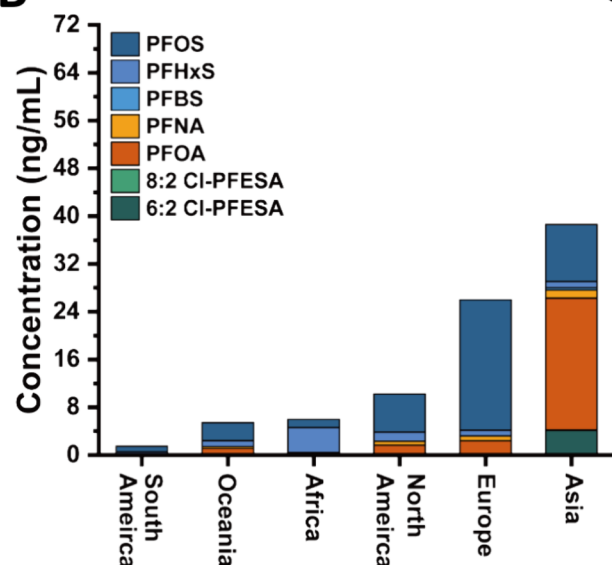
A reagent blank comprising Milli-Q water and two procedural recovery tubes with real serum samples were analyzed at the same time for each batch experiment of 30 to 45 samples. With the

exception that procedural recovery samples were spiked with 10 ng of each target native PFAS standard (in addition to internal standards), all other procedures were the same as those for real samples. Concentrations of PFAS in all reagent blanks were less than the LOD, obviating any need for blank correction. The LOD was determined

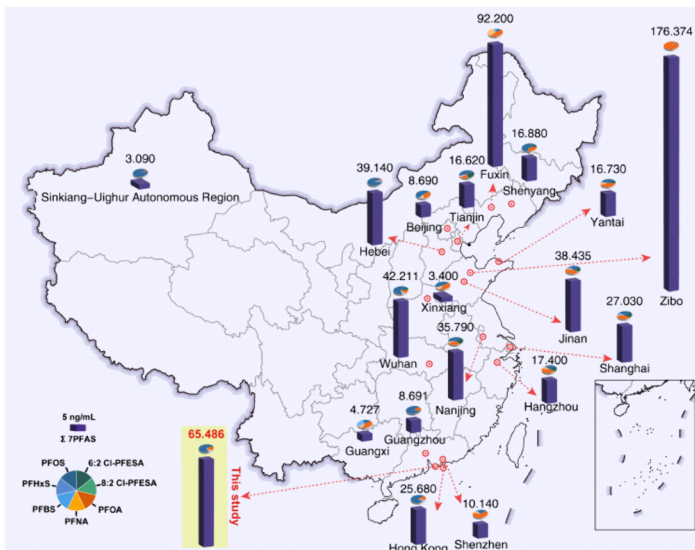
A



B



C



**Figure 2.** Comparison of PFAS concentrations (mean or median or GM) in human serum samples worldwide (A), by continents (B), and in China (C).

with a signal-to-noise ratio of 3:1 based on the lowest concentration calibration standard leading to LOD values in the range of 0.279–79.508 ng/L (Table S5). Our calibration covered a concentration range of 0.1–50 ng/mL with excellent linearity exemplified by regression coefficients ( $r$ ) > 0.99 for each target PFAS. Seven target PFAS were recovered at 71–97% of their spiked concentrations in these procedural recovery samples, and recoveries of their internal standards ranged from 49% to 107% (Table S5).

## 2.6. Quantification of Biomarkers

Three biomarkers were detected through relative kits (Nanjing Jiancheng Bioengineering Institute, China). Malonaldehyde (MDA) levels were determined by the thiobarbituric acid (TBA) method. As condensation can happen between MDA and TBA, it produces red products that have the biggest absorption peak under a wavelength of

530 nm, and immunoglobulin M (IgM) and C-reaction protein (CRP) were measured by immunoturbidimetry. IgM can have an antigen–antibody reaction with their corresponding antibody and form immune complexes, and the change of turbidity can be detected under a wavelength of 340 nm. The CRP will react and agglutinate with its antibody that was coated on latex particles, and its antigen–antibody complexes could have a great absorption value under a 562 nm wavelength.

## 2.7. Statistical Analysis

In this study, statistical analyses were performed with SPSS 23.0 (SPSS, Inc., Chicago, IL) and Microsoft Excel 2024 (Microsoft, WA). For the purpose of descriptive statistics, PFAS concentrations below the LOD were assumed to equal to LOD divided by the square root of 2.<sup>9</sup> All data were verified for normality and homogeneity of variance



using the Kolmogorov–Smirnov one sample test and Levene's test. Data are shown as the arithmetic mean  $\pm$  the standard error (SE). Differences in concentrations of PFAS in serum samples between ages and between gender were assessed using a one-way analysis of variance (ANOVA) followed by Duncan post hoc test or independent samples *t* tests. Pearson correlation coefficients were used to analyze the relationship between two sets of data (with PFAS concentrations and biomarker concentrations  $\log_{10}$  transformed prior to analysis). The level for statistical significance was set at  $p < 0.05$  and  $p < 0.01$ , which is indicated by one asterisk and two asterisks in the figures, respectively. All figures in this study were drawn using OriginPro 2024.

### 3. RESULTS AND DISCUSSION

#### 3.1. Concentrations of PFAS in Human Serum

In this study, seven target PFAS were detected in over 99% human serum samples, with an average concentration of 65.486 ng/mL for  $\Sigma_7$ PFAS (Table S5). On the whole, the average concentrations (mean  $\pm$  SE) of 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFOA, PFNA, PFBS, PFHxS, and PFOS in all human serum samples were  $3.561 \pm 0.23$ ,  $0.048 \pm 0.005$ ,  $10.918 \pm 0.449$ ,  $3.464 \pm 0.146$ ,  $0.063 \pm 0.008$ ,  $1.321 \pm 0.092$ , and  $46.110 \pm 2.789$  ng/mL (Figure 1A), with detection rates of 100% for all individual compounds, except for 8:2 Cl-PFESA and PFBS which were 99% (Table S5). Compared to previous studies, the detection rate of the present study are relatively high.<sup>36</sup> PFOS and PFOA are the top two major pollutants with profile abundances of 70% and 17% for all serum samples in this study, followed by 6:2 Cl-PFESA, and similar distributions were observed for males and females (Figure S1). This is consistent with prior research that examined 12 PFAS in human serum samples from Zhejiang, China, which identified PFOS, PFOA, and 6:2 Cl-PFESA as the first three compounds with the highest mean concentrations.<sup>37</sup> Simultaneously, based on the seven target PFAS compounds,  $\Sigma_3$ PFASs (47.494 ng/mL) were the dominated pollutants, followed by  $\Sigma_2$ PFCAs (14.382 ng/mL) and  $\Sigma_2$ F-53B (3.609 ng/mL) (Figure 1B).

The serum concentration of  $\Sigma_7$ PFAS was significantly higher ( $p < 0.05$ ) in males (mean, 73.522 ng/mL) than in females (mean, 49.885 ng/mL) in this study (Figure 1C). This aligns with previous studies indicating that males usually faces higher exposure of PFAS than females.<sup>21</sup> The disparity we observed might be attributed to a combination of distinct exposure pathways and metabolic differences between males and females, which may include lifestyle factors, occupational exposure patterns, and variations in body composition and metabolism. For individual compounds, significantly higher ( $p < 0.01$ ) concentrations of PFOA (male (M) = 11.811 ng/mL; female (F) = 9.185 ng/mL), PFHxS (M = 1.653 ng/mL; F = 0.677 ng/mL), and PFOS (M = 52,717 ng/mL; F = 33.282 ng/mL) were observed in the male than in the female, while other PFAS did not show a statistically significant difference between genders (Figure 1D, Table S5). Meanwhile, there were substantial distinctions between  $\Sigma_2$ PFCAs (M = 15.471 ng/mL; F = 12.270 ng/mL) and  $\Sigma_3$ PFASs (M = 54.432 ng/mL; F = 34.026 ng/mL) in terms of gender, with statistically significant differences ( $p < 0.01$ ) (Figure 1D, Table S5). This again highlights the need for gender-specific risk assessments and tailored public health interventions.

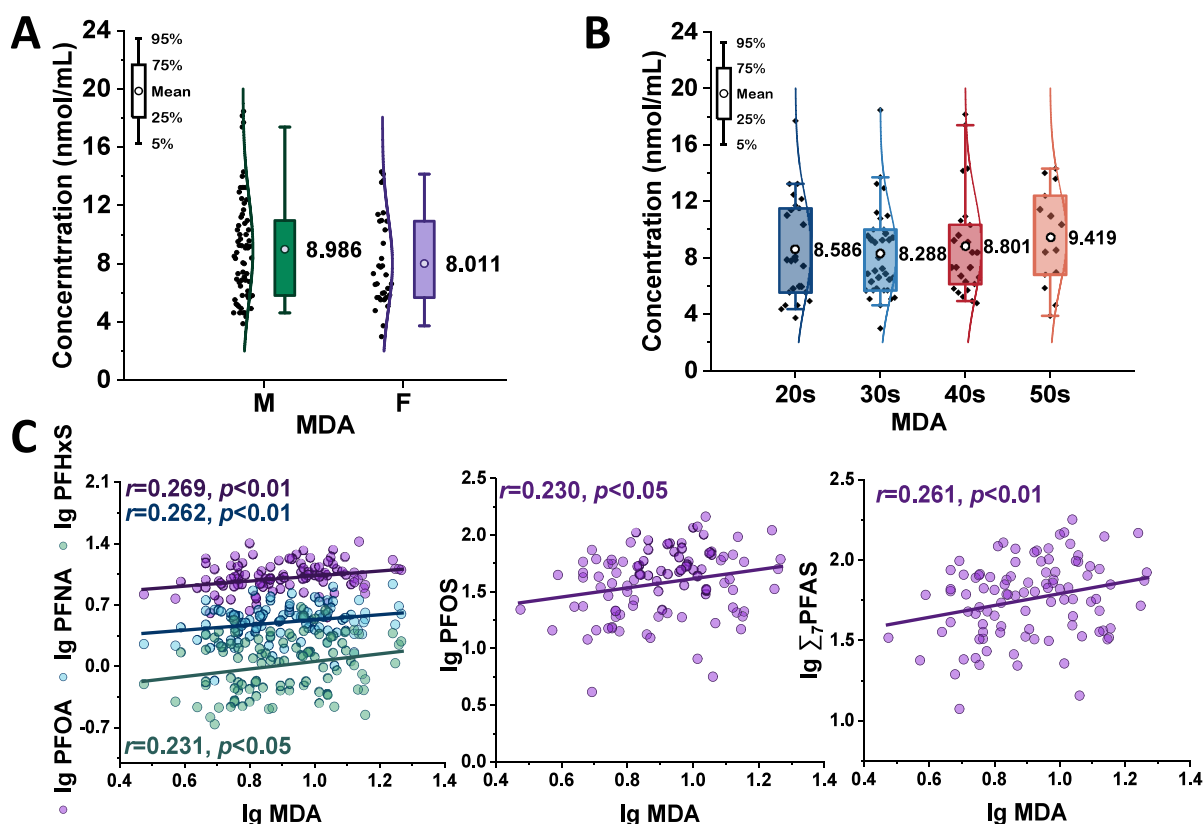
We also analyzed the differences in serum PFAS levels across various age groups to explore the accumulation of PFAS by age (Table S5). From the results, the serum levels of  $\Sigma_7$ PFAS in the age groups of 30s (68.509 ng/mL), 40s (71.358 ng/mL),

and 50s (84.723 ng/mL) were all significantly higher ( $p < 0.01$ ) compared to that in the 20s (44.373 ng/mL) age group (Figure 1E), which indicates that PFAS can possibly be accumulated by age in the human body. Corresponding to  $\Sigma_7$ PFAS,  $\Sigma_3$ PFASs and  $\Sigma_2$ F-53B also showed the same tendency in age group distribution, with statistically significant distinctions ( $p < 0.01$  or  $p < 0.05$ ) (Figure 1E). Although an increasing trend by age was noted for  $\Sigma_2$ PFCAs, statistical significance ( $p < 0.01$ ) was observed only between the 50s (16.538 ng/mL) and 20s (12.580 ng/mL) (Figure 1E). Regarding specific compounds, except for PFOA, which presented no significant difference between any age groups, all the other six target PFAS display an increasing trend and showed a significant difference across age groups more or less, which implies that the levels of these PFAS compounds increase with age. However, this could be indicative of various factors, such as longer exposure times leading to higher accumulation in older age groups, different exposure sources or behaviors associated with different age groups, or even physiological differences that affect how PFAS are processed or eliminated by the body. Thus, further studies are necessary to identify the potential impact factors.

#### 3.2. Comparison of Serum PFAS in China and Countries Worldwide

We have compared previously published data on PFAS concentrations in human serum samples from 1983 to 2021 across 31 countries worldwide (Table S6). The results revealed significant regional disparity in weighted average or median serum concentrations of  $\Sigma_7$ PFAS ranging from 0.810 to 64.500 ng/mL (Figure 2A). To be specific, based on the previous results, the top ten countries with the highest  $\Sigma_7$ PFAS concentrations were Belgium, Greenland, China, France, Finland, Poland, Japan, Spain, the United States, and Denmark, in that order, with weighted average  $\Sigma_7$ PFAS concentrations of 64.500 ng/mL, 40.800 ng/mL, 40.297 ng/mL, 27.900 ng/mL, 20.590 ng/mL, 20.190 ng/mL, 16.390 ng/mL, 13.800 ng/mL, 10.390 ng/mL, and 10.360 ng/mL, respectively (Figure 2A). Interestingly, 90% of the top countries with the highest  $\Sigma_7$ PFAS concentrations are located in Asia and Europe, with most of them recognized as industrialized regions. On a continental scale, the highest weighted average concentration of  $\Sigma_7$ PFAS was observed in Asia, with 38.597 ng/mL, followed by Europe at 25.995 ng/mL and North America at 10.202 ng/mL, and in contrast, South America had the lowest concentration at 1.500 ng/mL (Figure 2B). Both distributions observed at country and continental scales align with the global PFAS production patterns compiled by the USA EPA, which indicates that the major companies producing and supplying the global market with PFAS are predominantly located in Europe and Asia, including 3M plants in both Belgium and North America.<sup>38</sup>

Simultaneously, we have also compared the PFAS concentrations of serum samples collected during 2001 to 2021 across 18 cities or provinces (Table S7). The results also presented a wide variation in the average or median concentrations of  $\Sigma_7$ PFAS in serum across different cities with a range of 3.090 to 176.374 ng/mL (Figure 2C). The highest weighted average concentration of  $\Sigma_7$ PFAS was presented in Zibo, Shandong at 135.925 ng/mL, followed by Fuxing, Liaoning (92.200 ng/mL), Wuhan, Hubei (42.211 ng/mL), Hebei (39.140 ng/mL), and Jinan, Shandong (38.435 ng/mL). The highest weighted average concentrations of



**Figure 3.** Mean concentrations of MDA across gender differences in human serum samples (M = male, F = female) (A); concentration distribution of MDA across age groups in human serum samples (B); correlation (log<sub>10</sub> transformed) of individual PFAS and Σ<sub>7</sub>-PFAS with MDA in the human serum samples (C).

Σ<sub>7</sub>-PFAS in Zibo are likely due to extensive industrial activities like a fluorochemical plant in the region, which contribute to elevated PFAS levels in local rivers and human exposure.<sup>21,39</sup> The median concentrations of Σ<sub>7</sub>-PFAS in Guangzhou and Shenzhen were relatively low at 8.691 and 10.140 ng/mL, separately. However, the Σ<sub>7</sub>-PFAS concentration in this study (mean, 65.486 ng/mL; median, 61.057 ng/mL) is relatively higher than the levels reported a decade ago in these two cities of Guangdong. This increase is likely attributable to sampling in highly industrialized areas in this study, as well as the escalated industrial usage and pervasive presence of PFAS in consumer products, which are particularly notable in a rapidly developing metropolis such as Shenzhen. When the results above are combined, it suggests that human PFAS exposure levels may be linked to industrial activities and the locations of PFAS production. This emphasizes the need for strategies to cut PFAS emissions and exposure in these areas, possibly through regulations, industry changes, and safer chemical options.

### 3.3. Oxidative Stress of MDA in Human Serum

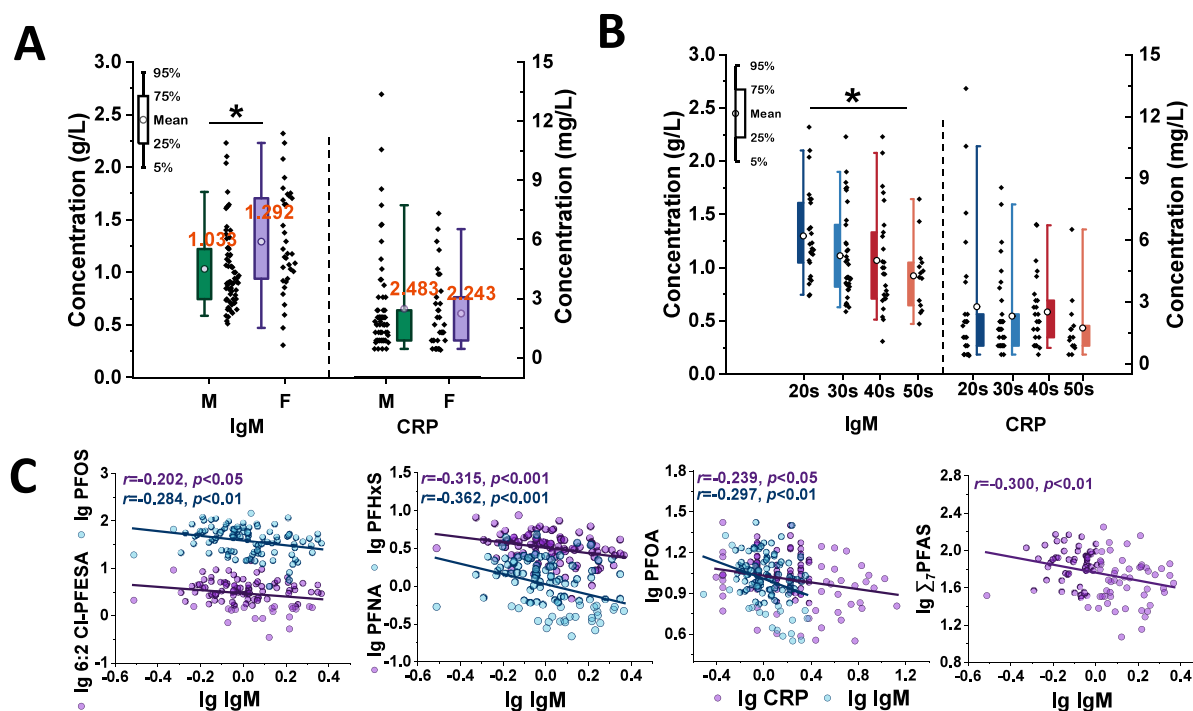
As a critical initiator of immune responses, a biomarker of oxidative stress was detected. In this study, the mean level of MDA in serum was 8.654 nmol/mL (Table S5). When nonsignificant differences were ignored, the mean serum MDA concentrations in males (8.986 nmol/mL) were higher than those in females (8.011 nmol/mL) (Figure 3A), which was consistent with the result of serum Σ<sub>7</sub>-PFAS level distribution among gender that was also higher in males (Figure 1C). Moreover, even though the mean MDA level of the 50s age group (9.419 nmol/mL) was apparently higher than those of

younger age groups (20s, 8.586 nmol/mL; 30s, 8.288 nmol/mL; 40s, 8.801 nmol/mL), no significant difference was observed for the MDA distribution across age groups (Figure 3B). The lack of significant age-related differences in MDA levels contrasts with some studies that suggest age as a factor in PFAS exposure and oxidative stress,<sup>40,41</sup> indicating a need for further investigation into the role of age in the context of oxidative stress of MDA.

In the study, a positive correlation was observed between the serum Σ<sub>7</sub>-PFAS concentration and the serum MDA level with statistical significance ( $p < 0.01$ ) (Figure 3C). This is consistent with previous studies indicating that higher PFAS levels are associated with higher levels of oxidative stress.<sup>42–44</sup> The findings of this study are consistent with previous research that has established PFAS as contributors to oxidative stress, as indicated by the correlation with MDA levels.<sup>41,45</sup> An analysis of the correlation between seven individual PFAS compounds and MDA revealed that the concentrations of PFOA, PFNA, PFHxS, and PFOS were all significantly ( $p < 0.01$  or  $p < 0.05$ ) and positively correlated with the level of MDA in human serum samples from this study (Figure 3C), suggesting again that these specific PFAS compounds might contribute to oxidative stress.

### 3.4. Immune Interference in Human Serum

To evaluate immune interference, this study detected the immunologic factors IgM and CRP in 100 samples. The concentrations (mean ± SE) were 1.121 ± 0.044 g/L for IgM and 2.402 ± 0.226 mg/L for CRP, respectively (Table S5). The mean serum IgM concentration in males (1.033 g/L) was significantly lower ( $p < 0.05$ ) than that in females (1.292 g/L),



**Figure 4.** Mean concentrations of IgM and CRP across gender differences in human serum samples (M = male, F = female) (A); the concentration distribution of IgM and CRP across age groups in human serum samples (B); correlation (log<sub>10</sub> transformed) of individual PFAS and Σ<sub>7</sub>PFAS with IgM and CRP in the human serum samples (C). The asterisk (\*,  $p < 0.05$ ) indicates a significant difference.

while no significant difference was observed in CRP levels between genders (Figure 4A). In addition, we observed a clear decrease in IgM levels between age groups from the 20s to the 50s, with a significant difference observed only between the 20s and the 50s ( $p < 0.05$ ); however, no significant difference was observed in CRP levels between age groups (Figure 4B). Thus, increasing age was not shown to clearly influence the immune system in the present study.

In the present study, the concentration of Σ<sub>7</sub>PFAS showed a significant and negative correlation with IgM levels ( $p < 0.01$ ) (Figure 4C). The results are consistent with previous studies that have indicated PFAS can modulate immune function.<sup>46,47</sup> Previous studies have also indicated that PFAS, including PFOA, PFOS, and PFBS studied in the present study, can decrease NF-κB activation, which directly suppresses cytokine secretion by immune cells.<sup>48</sup> For individual compounds, the concentrations of 6:2 Cl-PFESA, PFOA, PFNA, PFHxS, and PFOS were all negatively correlated with IgM levels, with statistical significance ( $p < 0.001$ ,  $p < 0.01$ , or  $p < 0.05$ ). Additionally, serum PFOA levels exhibited a significant negative correlation ( $p < 0.05$ ) with CRP levels (Figure 4C); this result echos a previous study that reported modest downregulation of CRP was associated with the blood concentration of PFOA.<sup>49</sup> Dewitt et al. have reported that exposure to PFOA in mice can lead to a decrease in IgM antibody titers, which is associated with their adaptive immune response.<sup>50</sup> The negative correlation between PFAS and IgM levels is also supported by previous research, suggesting that PFAS exposure can lead to immunosuppression.<sup>27,51</sup> Furthermore, Salihovic et al. has found plasma PFOA are closely negatively correlated with CRP levels.<sup>52</sup> Our results suggest that exposure to PFAS may reduce the expression of IgM and CRP, indicating potential immunosuppression and an

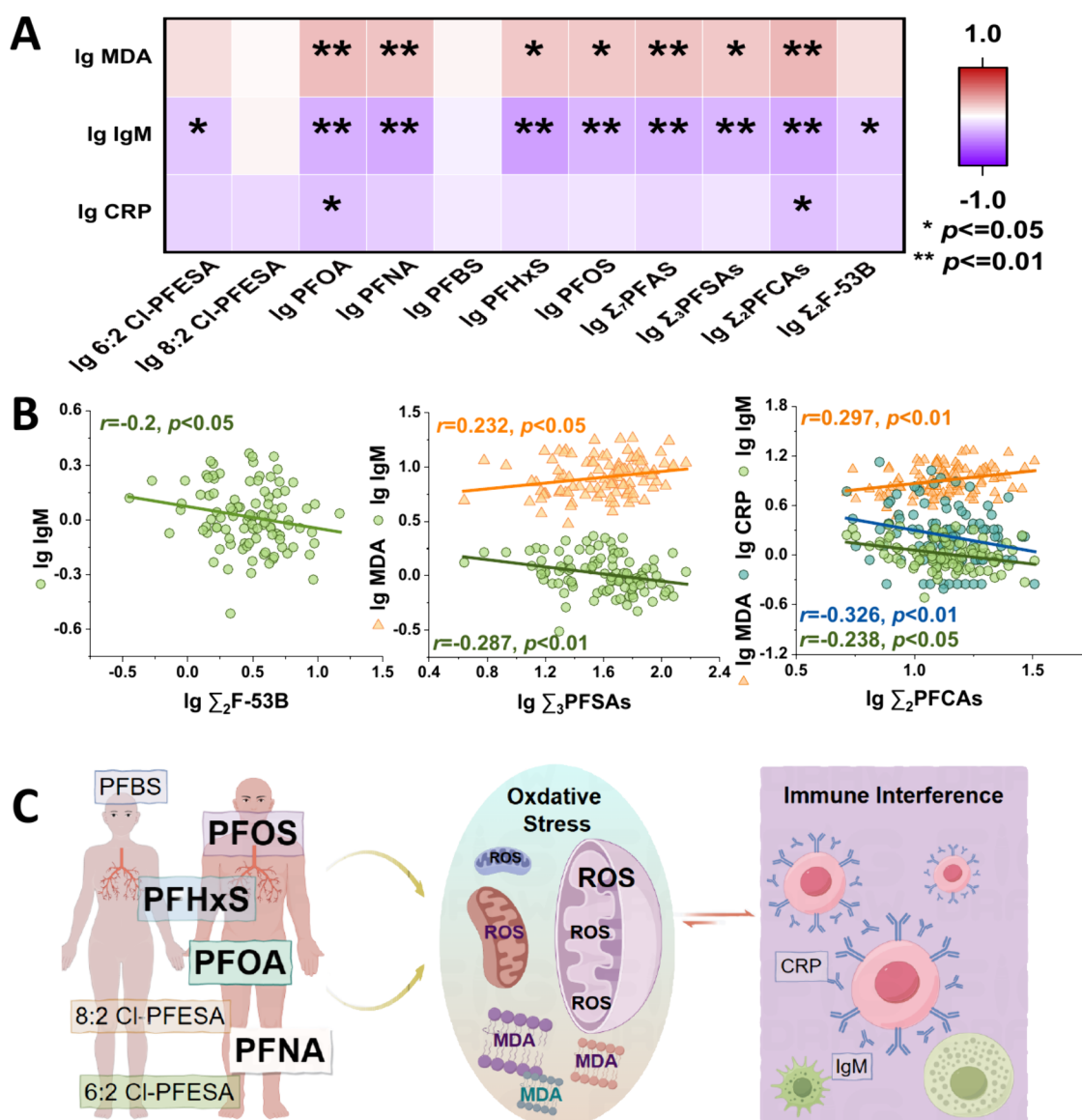
associated health risk of immune interference in the human body.

### 3.5. A Holistic View of Correlations for PFAS with Human Health Risk

In this study, we explored the interrelationships among seven serum PFAS compounds, their correlations with three biomarkers, and the relationships among the biomarkers themselves (Figure S2). From the results, strong positive relationships were observed among each of the seven PFAS, as well as the subgroups of Σ<sub>7</sub>PFAS, Σ<sub>3</sub>PFASs, Σ<sub>2</sub>PFCAs, and Σ<sub>2</sub>F-53B, which implies that these PFAS compounds might share common sources, exposure pathways, or metabolic behaviors in the body, which echo other previous studies again.<sup>26,27,53</sup> Additionally, it suggests that individuals exposed to one type of PFAS may likely be exposed to others, highlighting the cumulative presence of multiple PFAS and their potential collective impact on health.

The correlation analysis of serum concentrations of the target PFAS and three biomarkers revealed that, among the seven PFAS compounds, PFOA, PFNA, PFHxS, and PFOS were the primary contributors to the increase of the MDA levels, indicating elevated oxidative stress (Figure 5A). Their significant presence in the human body suggests a strong link between these specific PFAS and oxidative damage, which may have implications for various health outcomes. Coincidentally, these four PFAS compounds showed a significant positive correlation with serum levels of the immune index IgM. Additionally, 6:2 Cl-PFESA also contributed to the increase in IgM, and PFOA was associated with increased levels of CRP in serum (Figure 5A). Besides, significantly negative correlations were observed between the concentrations of MDA and IgM (Figure S2), indicating a potential relationship of oxidative stress and immune expression. We have also observed a positive correlation ( $p < 0.05$  or  $p < 0.01$ ) between





**Figure 5.** Pearson correlations (log<sub>10</sub> transformed) of PFAS and biomarkers (A); correlation (log<sub>10</sub> transformed) of Σ<sub>3</sub>PFSAs, Σ<sub>2</sub>PFCAs, and Σ<sub>2</sub>F-53B with IgM and CRP in the human serum samples (B); the possible mechanism indicated according all of the results of the present study (C).

concentrations of Σ<sub>3</sub>PFSAs and Σ<sub>2</sub>PFCAs with MDA, except Σ<sub>2</sub>F-53B. However, concentrations of all the subgroups showed significantly negative relationships with the concentrations of IgM (Figure 5B).

When the above results are combined, it suggests that human exposure to PFAS (particularly PFOA, PFNA, PFHxS, and PFOS) may induce oxidative stress, which could, in turn, affect immune function or lead to immunosuppression (Figure 5C). The correlations between these PFAS compounds and immune-related biomarkers, such as IgM and CRP, highlight the potential health risks associated with PFAS exposure, emphasizing the need for further investigation into their impacts on immune interference and overall health.

#### 4. CONCLUSIONS

Based on the findings of this study, human exposure to PFAS, especially in industrialized areas, presents notable implications for public health due to its association with oxidative stress and immune interference. High serum levels of seven PFAS compounds in this study have been detected, with PFOS

being the most prevalent, thus implying the necessity of priority control. The higher human serum concentrations of Σ<sub>7</sub>PFAS in industrialized nations warrant further investigation into the impact of PFAS on human health and the environment. Statistically significant associations between Σ<sub>7</sub>PFAS and increased levels of MDA support the hypothesis that PFAS exposure can elevate oxidative stress in humans, potentially leading to cellular damage. Among the seven PFAS compounds, PFOA, PFNA, PFHxS, and PFOS were the primary contributors to the increase of the MDA levels.

Furthermore, the study revealed significant correlations between PFAS concentrations and immune biomarkers IgM and CRP. Notably, elevated PFAS levels, particularly Σ<sub>7</sub>PFAS, were linked to a decrease in the level of IgM, suggesting a potential immunosuppressive effect. Gender differences were also observed, with males exhibiting higher serum levels of certain PFAS and corresponding MDA levels, implying sex-based differences in PFAS accumulation and its health impacts. Age also appeared to be a factor as older participants tended to



show higher PFAS levels, which may reflect cumulative exposure over time.

The high detection rates of PFAS in serum, particularly in industrial areas, underscore the need for regulatory actions to control emissions and exposure to these persistent chemicals. Future studies should explore the underlying mechanisms of PFAS-related immune modulation and oxidative stress to further understand the potential health risks, with particular attention being paid to vulnerable populations and high-exposure areas.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/envhealth.4c00224>.

Additional information, including compound information, participants' demographic information, instrumental parameters, detailed research data, and related figures (PDF)

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### Notes

The authors declare no competing financial interest.

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